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EXAMINER

LILLING, HERBERT J

ART UNIT	PAPER NUMBER
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1657

NOTIFICATION DATE	DELIVERY MODE
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ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 10/583,587	Applicant(s) CHEN, XUEJUN	
	Examiner HERBERT J. LILLING	Art Unit 1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 19 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 8-18 is/are rejected.
- 7) ☒ Claim(s) 7 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>June 19, 2006</u> | 6) <input type="checkbox"/> Other: _____ |

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1. Receipt is acknowledged of a preliminary amendment and a prior art information disclosure statement filed June 19, 2006.

2. Claims 1-18 are now pending in this application which is a 371 of PCT/CN03/01092 FILED 12/19/2003.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6 and 8-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over George et al, U.S. 5,977,250 alone, further in view of or Escalona et al., U.S. 5,536,419; Marchessault et al U.S. 5,454,456; Ramsay et al, U.S. 5,110,980; or/and Holmes et al U.S.4,910,145.

The rejections of the claims have been based essentially on basic common known processing conditions in the field of fermentation recovery of extracts of polymeric polyhydroxyalkanoates in light of the Supreme Court's recent decision in KSR International Co. v. Teleflex Inc (TFX), 82 USPQ2d 1385 (2007) based on the reasoning may still include the established Court of Appeals for the Federal Circuit standard that a claimed invention may be obvious if the examiner identifies a prior art teaching, suggestion, or motivation (TSM) to make it. However, the Guidelines explain that there is no requirement that patent examiners use the TSM approach in order to make a proper obviousness rejection. Furthermore, the Guidelines point out that even if the TSM approach cannot be applied to a claimed invention that invention may still be found obvious.

If there are any differences with respect to the claimed subject matter and the general knowledge pertaining to the art in the area, that these differences would have been prima facie obvious to one of ordinary skilled in the pertinent art whether it was based on the art of record or claimed subject would have obvious for the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results and the combination must do more than yield a predictable result.

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The Supreme stated the following:

“When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, 35 U.S.C. 103 bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve a similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.”

Thus, this Examiner will give Applicant an opportunity to argue, show in the specification ~~patentable~~ improvement(s) or amend the specification to overcome the following rationale for the rejections of the instant claims.

The KSR Decision requires rationales to support the rejections under 35 USC 103. The first issue is to analyze the Graham factual inquires as noted above for obviousness based of the prior art but the prior art is not limited to references but includes the basic knowledge and understanding of one skill in the pertinent art. Thus, the prior art alone or in combination does not have to teach or suggest or motivate one all of the limitations of the claimed limitations but there must be some rationale to explain these differences would have been obvious to one of ordinary skill in the art.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) according to the above factors which as indicated by the Supreme Court is not limited to an obviousness rejection of the claims for the following factors:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The first issue is consideration of the instant Invention which is drawn to one independent claim which recites the following:

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Claim 1- A method for directly separating and purifying polyhydroxyalkanoates

in cells from a bacterial fermentation liquid, which comprises the steps of:

a) physically pretreating a fermentation liquid containing cells to cause the walls of the cells to break;

b) adjusting the pH value of the pretreated fermentation liquid from step a) to an alkaline condition;

c) adding anionic surfactant to the solution of step b) and subjecting the solution to agitation;

d) separating and extracting coagulated precipitate from the solution in step c);

e) washing and drying the coagulated precipitate,

wherein the physical breaking the cell walls, and wherein steps b) and c) are interchangeable.

Prior Art

George et al. U.S. 5,977,250 discloses the following:

Further precautions desirable for avoidance of crystallisation include keeping the suspension at a low ionic strength, keeping the suspension aseptic, not using hypochlorite and keeping the suspension within 2 pH units of neutrality. To keep down the ionic strength the production of the biomass is preferably in chemostat conditions maintaining the pH by addition of alkali in response to electrochemical measurement.

George et al teaches the surfactant can be anionic, cationic, non-ionic, zwitterionic or contain hydrophilic groups of more than one type. The hydrophilic part of the surfactant preferably contains at least 8, especially 12-20, carbon atoms per hydrophilic group. It may be (almost) wholly aromatic as in sulphonated naphthalenes and naphthyl methanes; or partly aromatic as in alkyl benzene

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sulphonates or ethoxylates; or wholly aliphatic. Very suitably the surfactant contains a linear alkyl group. If the surfactant is cationic, preferably its hydrophilic part is quaternary ammonium, based for example on tri C.sub.1 - C.sub.4 alkylammonium. If it is anionic, the hydrophilic group is typically sulphate, sulphonate, carboxylate, phosphate or phosphonate. If it is non-ionic, it may be for example an ethoxylate, for example, an alkyl ethoxylate containing 7 to 16 (especially 12 to 16) alkyl carbons and up to 100 (especially about 20) ethoxylate units, or a block copolymer of ethylene oxide and propylene oxide or an alkylphenyl-ethoxylate (especially nonyl phenol with about 30 ethoxylate units). Suitable cationic surfactants include, typically as chloride or bromide: dodecyl-, tetradecyl- and cetyltrimethyl-ammonium, cetyldimethyl-ethylammonium, dodecyl-, tetradecyl- and hexadecyl-benzyltrimethylammonium, benzalkonium, benzethonium, methylbenzethonium and cetylpyridinium. Suitable anionics include, typically as sodium or ammonium salts: dodecyl sulphate, N-lauroyl-sarcosinate, dioctyl-sulfosuccinate, cholate, deoxycholate, laurate, myristate, palmitate, and stearate. Suitable non-ionics include sorbitan monopalmitate, alkylglucosides and nonyl phenyl-ethoxylates. The cationic preferred is cetyltrimethyl-ammonium bromide. Sodium or deoxycholate, dodecyl sulphate, N-lauroylsarcosinate and dioctylsulfo-succinate are preferred as anionics ammonium. Ammonium forms of the anionics are preferred when it is desired to avoid introducing mineral matter

Further precautions desirable for avoidance of crystallisation include keeping the suspension at a low ionic strength, keeping the suspension aseptic, not using hypochlorite and keeping the suspension within 2 pH units of neutrality. To keep down the ionic strength the production of the biomass is preferably in chemostat conditions maintaining the pH by addition of alkali in response to electrochemical measurement.

A further expedient proposed for NPCM removal is treatment with a surfactant. U.S. Pat No. 5,110,980) it is disclosed that biomass that has been treated with anionic surfactant and separated therefrom is more fully freed of NPCM by hypochlorite digestion.

EXAMPLE 4**Preparation of small-particle latex**

In a stirred fed batch fermenter *Alcaligenes eutrophus* was grown on glucose as carbon source, then fermented with glucose and propionic acid under phosphorus starvation to effect accumulation of a PHA consisting of HB and HV units in the molar ratio 85:15. To the fermenter product at ambient temperature sodium N-lauroylsarcosinate (6.5% w/w on the PHA) was added and mixed in. The mixture was passed once through a French pressure cell (105.6 kg/cm²) to disrupt the cells, then adjusted to pH 6.8 by addition of 5M potassium hydroxide. Chelator DTPA (1% w/v), sodium hydrogen phosphates pH 6.8 and silicone antifoam (100 ppm w/v) were stirred in. The mixture was heated to 80.degree. C. Hydrogen peroxide 60% w/v solution was added to provide 3% w/v H₂O₂ in the mixture. The mixture was stirred at 80.degree. C. for 12 h, with a further hydrogen peroxide addition at 3.5 h to replenish the 3% w/v level, and with periodic adjustment of pH to 6.8. The mixture was then passed to a tangential flow filter in which soluble material was separated, leaving a stable latex of PHA content 400 g/l.

In the resulting latex the average particle size was 0.35 .mu.m. The particles were examined by density measurement and found to be less than 1% w/w crystalline. The PHA contained less than 2% w/w of NPCM residues.

George et al teaches in this example a preparation of a PHA which fermented product is processed with an anionic surfactant, sodium N-lauroylsarcosinate, and the physical disruption through a French pressure cell whereby the adjustment at a pH of 6.8 with potassium hydroxide.

George et al further teaches:

If a treatment step before the claimed surfactant and oxidant treatment is used, it is preferably at not over 50.degree. C., for example:

- (a) mechanical homogenisation suitably at high pressure using for example a French pressure cell and possibly in presence of surfactant;
- (b) oxidant/surfactant depolymerisation of nucleic acid; or
- (c) enzyme digestion to solubilise peptido-glycan by a cell wall lytic enzyme such as lysozyme. In general the process may include other steps previously proposed for such harvesting, for example heat-shocking the cells, cell wall breaking by audible sound, ultra-sound or high pressure homogenisation or

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even freeze-drying providing that substantial crystallisation or agglomeration is not provoked thereby.

The step of cell wall disruption by mechanical means in presence of surfactant is of more general application and constitutes a further aspect of the invention.

The reference does not employ a pH within an alkaline condition but states that the pH is within 2 units of neutrality.

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Ramsay et al, U.S. 5,110,980, "Separation of poly-.beta.-hydroxyalkanoic acid from microbial biomass"

Hypochlorite digestion of bacterial biomass to recover intracellular poly-.beta.-hydroxylalkanoic acid (PHA) has not been used on a large scale since it has been widely reported to severely degrade the polymer. The process of the invention proposes to optimize the initial biomass concentration, the digestion time and pH of the hypochlorite solution to minimize degradation. Consequently, PHA of up to 95% purity with an average molecular weight of 600,000 can be recovered from biomass initially containing PHA having a molecular weight of 1,200,000. By incorporating a pretreatment step with an anionic surfactant solution, PHA of 99% purity with a molecular weight of 1.20.times.10.sup.6 was obtained from biomass containing 57% PHA by weight with an initial molecular weight of 1.25.times.10.sup.6.

The weight average molecular weight of the chloroform extracted PHA was 1,200,000.

TABLE 1

pH				
8	10	12	13.6	
% purity	70	90	90	98
% PHA recovered	77	90	90	78
% MW*	36	54	37	21
MW (.times. 10.sup.5 g/mole)	4.36	6.50	4.39	2.50

% MW* is the percentage of the molecular weight of the PHA recovered to

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that of the chloroform extracted sample.

TABLE 7

	pH			
	8	9	10	11
% purity	77	81	82	84
% PHA recovered	67	67	62	59
% MW*	92.5	92	86	82
MW (.times. 10.sup.5 g/mole)	11.57	11.47	10.70	10.02

	pH		
	8	9	10
% purity	99	98	99
% PHA recovered	85	83	75
% MW*	82	90	96
MW (.times. 10.sup.5 g/mole)	10.01	11.50	12.00

In accordance with the invention, it has also been found that if a surfactant solution is added before **hypochlorite** treatment, the molecular weight of the recovered PHA may be conserved even further. For example, if a solution of 0.125% surfactant solution at pH 10 is followed by treatment with the 5.25% **hypochlorite** solution also at pH 10, 96% of the original molecular weight will be conserved to obtain 98% pure PHA having a molecular weight as high as 1,200,000. However, surfactant treatment on its own is insufficient to obtain PHA of high purity.

This reference teaches the general reaction conditions pertaining to pH and molecular weight whereby the purity of the PHA's increase with increasing pH as noted by Table 7.

Escalona et al., U.S. 5,536,419 "Procedure for extraction of polyhydroxyalkanoates from halophilic bacteria which contain them" teaches the following:

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"The cells are separated by centrifugation analogous to the previous case and resuspended in distilled water by intense agitation in a laboratory triturator. The suspension is heated at 65.degree. C. for 20 min. After this step, [the suspension] is centrifuged at 200 rpm for 5 min, followed by repetition of all the steps of the previous example as to the treatment with water, detergents, and successive centrifugations. A product is obtained with a yield of 97 to 99% and a purity of 98.99%."

Marchessault et al., U.S. 5,451,456

Marchessault et al teaches the following:

"b) Separation of PHA from Biomass

Two general approaches are taken to separate PHA from the rest of the bacterial biomass. **One is to break the cells and then use a series of separation steps to isolate the PHA granules.**

Separation may also be achieved by differential digestion using sodium hypochlorite. This method is based on the fact that PHB is degraded less by aqueous hypochlorite than other biomass components. Generally the procedure consists of contacting the PHA-containing biomass with an aqueous hypochlorite solution containing 5% titratable chlorine. **The residue may be purified by methods such as solvent washing, dialysis or recrystallization. In the past the main problem with this method was its severe effect on the polymer molecular weight.** Recently, however, methods for the optimization of hypochlorite digestion have been developed allowing the isolation of high molecular weight granules. **Pretreatment of biomass with nonionic or cationic surfactants enhances this process.**

Separation may also be achieved by enzymatic digestion in which an aqueous suspension of PHA-containing biomass is heat-shocked to between 100.degree.-150.degree. C. for a short period of time to denature protein, RNA and DNA and rupture the cell walls. **The pH is held at between 6 and 8 to avoid any PHA degradation.**

Sequential treatments with enzymes such as proteases and phospholipase are used to dissolve unwanted biomass. This is followed by washing with anionic surfactants such as sodium dodecylsulphate with or without EDTA.

Sonication or ultrasound can also be used to break cell walls in a preliminary step of granule isolation."

Holmes et al., U.S. 4,910,145

Holmes et discloses the following:

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Portions of the solid residue were re-suspended in water to give suspensions of solids content 50 g/l. To the suspensions there were then added commercial enzyme compositions and the suspensions were digested for 60 min at 50.degree. C. at pH values (adjusted as necessary by addition of sodium hydroxide) recommended by the enzyme suppliers

REJECTIONS:

George et al discloses processes for the separation and purification of PHA's obtained by fermentation in which the products are separated and purified which includes all of the process steps. George et al does not anticipate the claimed process steps whereby the cells are physically separated prior to the alkaline conditions. However, George et al teaches in Example 4, a step in which the fermented product is treated with an anionic surfactant and "the mixture was passed once through a French pressure cell (105.6 kg/cm.sup.2) to disrupt the cells, then adjusted to pH 6.8 by addition of 5M potassium hydroxide.

The above is considered to be within the scope of process step (b) whereby the pH is adjusted "to an alkaline condition" even though the solution has been maintained at a pH 6.8 since potassium hydroxide has been added. Especially in view of the following disclosure of George et al:

If a treatment step before the claimed surfactant and oxidant treatment is used, it is preferably at not over 50.degree. C., for example:

- (a) mechanical homogenisation suitably at high pressure using for example a French pressure cell and possibly in presence of surfactant;
- (b) oxidant/surfactant depolymerisation of nucleic acid; or
- (c) enzyme digestion to solubilise peptido-glycan by a cell wall lytic enzyme such as lysozyme. In general the process may include other steps previously proposed for such harvesting, for example heat-shocking the cells, cell wall breaking by audible sound, ultra-sound or high pressure homogenisation or even freeze-drying providing that substantial crystallisation or agglomeration is not provoked thereby.

The step of cell wall disruption by mechanical means in presence of surfactant is of more general application and constitutes a further aspect of the invention.

The issue is that one skilled in the art would reasonably expect to obtain the same results if the pretreatment of the fermented mixture is preliminary only with a physical treatment with any one of several physical methods which includes that of **Marchessault et al.**, U.S. 5,451,456.

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In addition, the pH of step (b) adjustment to higher pH, would have been prima facie obvious in view of Table 1 of Ramsay et al, U.S. 5,110,980 which reference teaches the effects of pH, time and other properties for the separation and purification of PHA's obtained from fermented products. It would have been prima facie obvious to one of ordinary skilled in the art to reasonably expect that as the pH is increased the purity of the PHA is increased. George does not teach the adjustment of the pH with sodium hydroxide, sodium bicarbonate or sodium carbonate or ammonia which would have been prima facie obvious to one of ordinary skilled in the art to substitute the above bases for that of potassium hydroxide absent unexpected patentable results and in view of Holmes et al., U.S. 4,910,145 which reference teaches a separation processes for PHA's from fermented solutions whereby sodium hydroxide would have been prima facie obvious to adjust the pH for that of potassium hydroxide in view of the following:

“ To the suspensions there were then added commercial enzyme compositions and the suspensions were digested for 60 min at 50.degree. C. at pH values (adjusted as necessary by addition of sodium hydroxide) recommended by the enzyme suppliers”

The mixture as required by Claim 1 is subjected to agitation of the mixture of the treated fermentation solution to agitation which is obvious in view of the disclosure of Escalona et al U.S. 5,536,419 which discloses the following:

The cells are separated by centrifugation analogous to the previous case and resuspended in distilled water by intense agitation in a laboratory triturator. The suspension is heated at 65.degree. C. for 20 min. After this step, [the suspension] is centrifuged at 200 rpm for 5 min, followed by repetition of all the steps of the previous example as to the treatment with water, detergents, and successive centrifugations. A product is obtained with a yield of 97 to 99% and a purity of 98.99%.

PHAs are accumulated intracellularly by many bacteria in the form of granules. The use of these polymers as thermoplastics requires their separation from the rest of the cellular materials with an adequate level of purity. For this, numerous methods have been described based on the use of solvents and selective precipitants, which methods extract the polymer PHA from the complex mixture which constitutes the cellular biomass by means of a process of dissolution and precipitation.

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If there are any differences with respect to the temperature, pH, anionic surfactant, agitation, coagulation or concentrations, the references are considered to render the instant claims unpatentable in view of KSR decision even if as stated above:

“...the prior art alone or in combination does not have to teach or suggest or motivate one all of the limitations of the claimed limitations ..”

Examiner will consider all arguments, amendments, declarations or any issues whereby there is persuasive reasoning the claimed subject matter have patentable differences over the art of record. As indicated, there are differences which differences have been considered not be justify patentable differences on the record.

4. Claim 7 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

5. **No claim is allowed.**

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to HERBERT J. LILLING whose telephone number is 571-272-0918. The examiner can normally be reached on WORK AT HOME MAXIFLEX.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JON WEBER can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit **1657**
August 3, 2008

/HERBERT J LILLING/
Primary Examiner Art Unit 1657